

WHAT IS CLAIMED IS:

1 1. A method of preventing or reducing intimal hyperplasia at the site of insult
2 to an internal structure, comprising contacting an exterior surface of the internal structure
3 with a delivery vehicle comprising at least a first and second intimal hyperplasia
4 preventing agents having a first and second release rate, respectively, wherein said drug
5 delivery vehicle is substantially flowable during application to said exterior surface and
6 substantially adheres to said exterior surface of said internal structure, and said drug
7 delivery vehicle releases said first and second agents in a time dependent manner and in
8 an amount effective to prevent or reduce said intimal hyperplasia.

1 2. The method of claim 1, wherein said delivery vehicle comprises said first
2 agent encapsulated in a reservoir having a first release rate, and a coating material which
3 incorporates said second agent and said encapsulated first agent.

1 3. The method of claim 2, wherein said reservoir is a monolithic structure or
2 a microparticle.

1 4. The method of claim 3, wherein said microparticle is a microsphere, a
2 microcapsule, or a liposome.

1 5. The method of claim 2, wherein said coating material is selected from the
2 group consisting of gels, hydrogel-forming materials, natural polymers, synthetic
3 polymers, synthetically modified polymers, fibrin sealants, biodegradable polymers, and
4 bioresorbable polymers.

1 6. The method of claim 5, wherein said gel is a thermoreversible gel.

1 7. The method of claim 6, wherein said gel is selected from the group
2 consisting of pluronics, collagen, gelatin, hyaluronic acid, polysaccharides, polyurethane
3 hydrogel, polyurethane-urea hydrogel, and combinations thereof.

1 8. The method of claim 5, wherein said hydrogel-forming material is selected
2 from the group consisting of polyacrylic acids, sodium carboxymethylcellulose, polyvinyl
3 alcohol, polyvinyl pyrrolidone, gelatin, carrageenan, hydroxyethylenemethacrylic acid,
4 and derivatives thereof

1 9. The method of claim 5, wherein said natural polymers are selected from
2 the group consisting of proteins and polysaccharides.

1 10. The method of claim 5, wherein said synthetic polymer is selected from
2 the group consisting of polyphosphazines, poly(vinyl alcohols), polyamides,
3 polycarbonates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene
4 oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides,
5 polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, poly(methyl
6 methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl
7 methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly (lauryl
8 methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate),
9 poly(isobutyl acrylate), poly(octadecyl acrylate) polyethylene, polypropylene,
10 poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl
11 acetate), polyvinyl chloride, polystyrene, polyvinyl pyrrolidone, pluronics,
12 polyvinylphenol, and copolymers thereof..

1 11. The method of claim 5, wherein said synthetically modified natural
2 polymers are selected from the group consisting of alkyl celluloses, hydroxyalkyl
3 celluloses, cellulose ethers, cellulose esters, and nitrocelluloses.

1 12. The method of claim 5, wherein said biodegradable polymers are selected
2 from the group consisting of polylactides, polyglycolides, poly(ethylene terephthalate),
3 poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), poly(lactide-co-
4 glycolide), polyanhydrides, polyorthoesters, and blends and copolymers thereof.

1 13. The method of claim 1, wherein said first and second agents are
2 independently selected from the group consisting of antithrombotics, antiinflammatories,
3 corticosteroids, antimicrotubule agents, antisense oligonucleotides, antineoplastics,
4 antioxidants, antiplatelets, calcium channel blockers, converting enzyme inhibitors,
5 cytokine inhibitors, growth factors, growth factor inhibitors, growth factor sequestering
6 agents, fibrosis inhibitors, immunosuppressives, tissue factor inhibitor, smooth muscle
7 inhibitors, sulfated proteoglycans, superoxide dismutase mimics, NO, NO precursors, and
8 combinations thereof.

1 14. The method of claim 1, wherein said first agent is released at a first
2 concentration and said second agent is released at a second concentration.

1 **15.** The method of claim 1, wherein said internal structure is selected from the
2 group consisting of a vascular system component, an intestinal system component, and a
3 urinary system component.

1 **16.** The method of claim 1, wherein said insult is a surgical insult.

1 **17.** The method of claim 16, wherein said internal structure is a vascular
2 structure and said surgical insult is selected from the group consisting of angioplasty,
3 vascular reconstructive surgery, heart valve replacement, heart transplantation, and
4 combinations thereof.

1 **18.** The method of claim 16, wherein said surgical insult comprises placing a
2 prosthesis at said site of said insult in said internal structure.

1 **19.** The method of claim 18, wherein said prosthesis is selected from the group
2 consisting of a stent, a graft, a valve, and combinations thereof.

1 **20.** The method of claim 18, further comprising contacting said prosthesis
2 with said delivery vehicle.

1 **21.** The method of claim 1, wherein said site of said insult comprises an
2 anastomosis.

1 **22.** The method of claim 1, wherein said insult is coronary artery bypass
2 grafting.

1 **23.** The method of claim 1, wherein said delivery vehicle comprises a first
2 coating material incorporating said first agent, and a second coating material
3 incorporating said second agent and layered over said first coating material.

1 **24.** The method of claim 23, wherein said first and second coating materials
2 are independently selected from the group consisting of gels, hydrogel-forming materials,
3 natural polymers, synthetic polymers, synthetically modified polymers, fibrin sealants,
4 biodegradable polymers, and bioresorbable polymers.

1 **25.** The method of claim 1, wherein said delivery vehicle comprises said first
2 agent encapsulated in a first microparticle and said second agent encapsulated in a second
3 microparticle.

1 **26.** The method of claim 25, wherein said first and second microparticles are
2 independently selected from the group consisting of microspheres, microcapsules, or
3 liposomes.

1 **27.** A method of preventing or reducing hyperplasia at a site of insult to a
2 vascular structure in a subject, wherein said insult is selected from the group consisting of
3 angioplasty, vascular reconstructive surgery, heart valve replacement, heart
4 transplantation, and combinations thereof, said method comprising contacting an exterior
5 surface of said vascular structure with a delivery vehicle comprising at least a first and
6 second intimal hyperplasia preventing agent having a first and second release rate,
7 respectively, wherein said drug delivery vehicle is substantially flowable during
8 application to said exterior surface and substantially adheres to said exterior surface of
9 said internal structure, and said drug delivery vehicle releases said first and second agents
10 in a time dependent manner and in an amount effective to prevent or reduce said intimal
11 hyperplasia.

1 **28.** The method of claim 27, wherein said delivery vehicle comprises said first
2 agent encapsulated in a reservoir having a first release rate, and a coating material which
3 incorporates said second agent and said encapsulated first agent.

1 **29.** The method of claim 28, wherein said reservoir is a monolithic structure or
2 a microparticle.

1 **30.** The method of claim 28, wherein said microparticle is a microsphere, a
2 microcapsule, or a liposome.

1 **31.** The method of claim 28, wherein said coating material is selected from the
2 group consisting of gels, hydrogel-forming materials, natural polymers, synthetic
3 polymers, synthetically modified polymers, fibrin sealants, biodegradable polymers, and
4 bioresorbable polymers.

1 **32.** The method of claim 27, wherein said delivery vehicle comprises a first
2 coating material incorporating said first agent, and a second coating material
3 incorporating said second agent and layered over said first coating material.

1 33. The method of claim 32, wherein said first and second coating materials
2 are independently selected from the group consisting of gels, hydrogel-forming materials,
3 natural polymers, synthetic polymers, synthetically modified polymers, fibrin sealants,
4 biodegradable polymers, and bioresorbable polymers.

1 34. The method of claim 27, wherein said delivery vehicle comprises said first
2 agent encapsulated in a first microparticle and said second agent encapsulated in a second
3 microparticle.

1 35. The method of claim 34, wherein said first and second microparticles are
2 independently selected from the group consisting of microspheres, microcapsules, and
3 liposomes.

1 36. The method of claim 27, wherein said vascular reconstructive surgery
2 comprises placing a prosthesis selected from the group consisting of a stent, graft, valve
3 or a combination thereof at the site of insult.

1 37. The method of claim 36, further comprising contacting said prosthesis
2 with said delivery vehicle.

1 38. A method of treating a disease state of an internal structure in a subject,
2 said method comprising:

3 surgically treating said disease state, thereby creating a surgical site; and
4 contacting an exterior surface of said internal structure contiguous with
5 said surgical site with a delivery vehicle comprising at least a first and second intimal
6 hyperplasia preventing agent having a first and second release rate, respectively, wherein
7 said drug delivery vehicle is substantially flowable during application to said exterior
8 surface and substantially adheres to said exterior surface of said internal structure, and
9 said drug delivery vehicle releases said first and second agents in a time dependent
10 manner and in an amount effective to prevent or reduce said intimal hyperplasia.

1 39. The method of claim 38, wherein said delivery vehicle comprises said first
2 agent encapsulated in a reservoir, and a coating material which incorporates said second
3 agent and said encapsulated first agent.

4 **40.** The method of claim 39, wherein said reservoir is a monolithic structure or
5 a microparticle.

1 **41.** The method of claim 40, wherein said microparticle is a microsphere, a
2 microcapsule, or a liposome.

1 **42.** The method of claim 39, wherein said coating material is selected from the
2 group consisting of gels, hydrogel-forming materials, natural polymers, synthetic
3 polymers, synthetically modified polymers, fibrin sealants, biodegradable polymers, and
4 bioresorbable polymers.

1 **43.** The method of claim 38, wherein said delivery vehicle comprises a first
2 coating material incorporating said first agent, and a second coating material
3 incorporating said second agent and layered over said first coating material.

1 **44.** The method of claim 43, wherein said first and second coating materials
2 are independently selected from the group consisting of gels, hydrogel-forming materials,
3 natural polymers, synthetic polymers, synthetically modified polymers, fibrin sealants,
4 biodegradable polymers, and bioresorbable polymers.

1 **45.** The method of claim 38, wherein said delivery vehicle comprises said first
2 agent encapsulated in a first microparticle and said second agent encapsulated in a second
3 microparticle.

1 **46.** The method of claim 45, wherein said first and second microparticles are
2 independently selected from the group consisting of microspheres, microcapsules, and
3 liposomes.

1 **47.** The method of claim 38, wherein said internal structure is a vascular
2 structure and said surgical procedure comprises angioplasty, vascular reconstructive
3 surgery, or combinations thereof.